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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/986,568	12/05/97	BACH J	040388/0110

HM11/0119

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/19/00

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 19

Application Number: 08/986,568
Filing Date: December 5, 1997
Appellant(s): Jean-Francois Bach and Lucienne Chatenoud

Stephen A. Bent
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 15, 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement that all claims stand or fall together is correct.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Chatenoud, L. et al. "Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice." Proceedings of the National Academy of Sciences (USA), vol. 91 (January 1994), pp. 123-127.

Hughes, C. et al. "Induction of T helper cell hyporesponsiveness in an experimental model of autoimmunity by using nonmitogenic anti-CD3 monoclonal antibody." The Journal of Immunology, vol. 153, no. 7 (October 1994), pp.3319-3325.

Racadot, E. et al. "Current concepts in the treatment of autoimmune diseases with monoclonal antibodies." Clinical Immunotherapeutics, vol. 1, no. 3 (May 1994), pp. 199-208.

Gussow, D. et al. "Humanization of monoclonal antibodies." Methods in Enzymology, vol. 203 (1991), pp. 99-121.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 U.S.C. § 102

1. Claims 1-2, 4-5, 9, 13 and 16-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chatenoud et al, as evidenced by Hughes et al, both of record.

The Chatenoud et al reference teaches the induction of antigen-specific unresponsiveness in NOD mice with full-blown disease (Abstract in particular), by injection of non-mitogenic anti-CD3 monoclonal antibody (mAb) $F(ab')_2$ fragments (page 123, subsection "Mice and Antibodies in particular), resulting in complete remission of overt disease (Abstract in particular). Although it is not specifically stated by Chatenoud et al, it is a fact well known in the art that $F(ab')_2$ fragments are non mitogenic because they do not induce the release of cytokines like intact mAbs do, as evidenced by Hughes et al's teachings using the same hamster monoclonal antibody, 2C11, for treatment in an unrelated autoimmune disease model (page 324, column 2 in particular). Chatenoud et al also teaches that the production of the anti-CD3 monoclonal antibody $F(ab')_2$ fragments is by "conventional pepsin digestion of the entire antibody molecule" (page 123, subsection "Mice and Antibodies in particular). The prior art teaching clearly anticipates the claimed invention.

Claim Rejections - 35 U.S.C. § 103

2. Claims 1-2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Racadot et al in view of Güssow et al and Chatenoud et al, all of record.

Chatenoud et al has been discussed supra. Chatenoud et al does not teach murine mAbs, humanized mAbs or the treatment of multiple sclerosis. Racadot et al teaches the treatment of multiple sclerosis in human patients with a dosage of 5 mg/day of a murine monoclonal antibody designated muromonab-CD3, a.k.a. OKT-3 (page 201, subsection 1.2.3 in particular). Racadot et al also teaches that the treatment is associated with a dramatic decrease in T cell count and the induction of clonal anergy (page 202, first new paragraph in column 2 in particular). However, Racadot et al teaches a drawback in the treatment in that all patients developed anti-murine Abs and some patients deteriorated during therapy (page 201, subsection 1.2.3 in particular) and a massive cytokine release (page 203, section 3 in particular). The skilled artisan would have readily recognized that the massive cytokine release associated with muromonab-CD3 treatment could be averted through the use of $F(ab')_2$ fragments of the mAb as taught by Chatenoud et al. The skilled artisan would have further recognized this still leaves the obstacle of the generation of anti-murine Abs in the patient because Güssow et al teaches that anti-murine Abs are still generated to the murine framework regions which remain in murine-human chimeric Abs (pages 99-100 in particular), which are essentially murine $F(ab')_2$ fragments fused to a human Fc region. Güssow et al teaches that this problem can be overcome by reshaping, humanization, of the murine Ab. It would have been prima facie obvious to a person of ordinary skill in the art at

the time the invention was made to modify the effective muromonab-CD3 mAb by humanization as taught by Güssow et al in order to alleviate the anti-murine complications taught by Racadot et al. One would have been further motivated to modify the humanized muromonab-CD3 by pepsin digestion of the entire humanized antibody to generate F(ab')2 fragments to use for treatment as taught by Chatenoud et al in order to eliminate the massive cytokine release associated with treatment using intact anti-CD3 antibodies. One would have been motivated to combine these references with a reasonable expectation of success by the teachings of Racadot et al and Chatenoud et al that anti-CD3 treatment induces tolerance in an ongoing autoimmune reaction and by the teachings of Chatenoud et al and Güssow et al which address the problems taught to be associated with intact muromonab-CD3 treatment by Racadot et al. Claim 6 is included because highly purified, endotoxin free reagents are routinely prepared in the art and are a well-known requirement for treatment of human patients. Claims 10 and 11 are included because, while none of the cited references specifically teach the treatment of rheumatoid arthritis or psoriasis, the anti-CD3 course of treatment does not require the administration of disease specific antigens or agents to the subject, nor is there a requirement of knowledge of the target antigen in the disease. Therefore, the skilled artisan would be able to reasonably predict that the method would be useful for the treatment of any autoimmune condition in which the involvement of T lymphocytes is a major factor in the etiology of the disease.

(11) Response to Argument

3. Claims 1-2, 4-5, 9, 13 and 16-18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chatenoud et al, as evidenced by Hughes et al, both of record.

Appellant argues that the Chatenoud et al reference could not be considered anticipatory because the reference shows, at best, a *transient* state of unrespsonsiveness, rather than the permanent disease remission claimed by Appellant. The Examiner respectfully disagrees with this position. The Chatenoud et al reference clearly shows (Figures 2b-d) and states (page 125, second column) that "a 5-day treatment with low-dose anti-CD3 (5 μg/day i.v.) or anti-CD3 $F(ab')_2$ (50 μg/day i.v.) Starting one day prior to the second CY injection (days 13-17) reproducibly prevented or reversed CY-induced diabetes" (emphases added for clarity). The only mention which could be found in the Chatenoud et al reference regarding *transient* effects is in the paragraph bridging page 126-127 in the disclosure that: "anti-CD3-induced remissions presented a number of unexpected features: (*I*) they developed over 2-4 weeks, suggesting active phenomena, (*ii*) the effect was durable (until sacrifice at >4 months), (*iii*) remission was associated with only partial and transient [underline added for clarity] T-cell depletion ($CD3^+$ cell counts returned to normal 15-20 days after the end of treatment), and (*iv*) clinical remission was maintained despite the presence of peripheral (but not invasive/destructive) insulitis...". The Chatenoud et al reference does not differentiate between the effects of intact anti-CD3 or anti-CD3 $F(ab')_2$ fragments. Appellant relies upon the declaration of Dr. Terry Strom, filed with the Appeal Brief, for disclosing that one of skill in the art at the time the invention was made, circa 1997, would not

have expected a durable, antigen-specific unresponsiveness to result from administering anti-CD3 antibody fragments, but could only arise from a release of immunoregulatory cytokines. This is not found to be persuasive because, as shown in the evidentiary reference of Hughes et al, that as early as 1994 it could be demonstrated that non-mitogenic fragments of anti-CD3 antibody, the same antibody as used in Chatenoud et al (mAb 145 2C11), could induce T cell hyporesponsiveness in vivo (page 3323, second column). Hughes et al further evidences that it was recognized in the art that mitogenic anti-CD3 antibodies are limited in the treatment of autoimmune disease because of the cytokine release and that the fragments "may have significant advantages over mitogenic mAbs as immunosuppressive reagents in the setting of autoimmune diseases" (page 3324, second column).

4. Claims 1-2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Racadot et al in view of Güssow et al and Chatenoud et al, all of record.

Appellant argues that Racadot et al does not use the same mAb as Chatenoud et al, does not teach durability of the effect of anti-CD3 treatment, and that Chatenoud et al cannot be applied to correct the deficiencies in Racadot et al. The Examiner acknowledges that the statement of Racadot et al using the same mAb as Chatenoud et al was in error and submits that the error was inadvertent. Appellant's analysis of Racadot et al is not persuasive. The Appellant points to a teaching in Racadot et al that treatment with muromonab-CD3 appears to be deleterious in patients (page 204, first column). It is respectfully submitted that Appellant has

taken this teaching out of context, as Racadot et al immediately qualifies this statement with the teaching, "[t]his may due to release of TNF, as TNF is involved in the pathophysiology of cerebral lesions" (page 204, first column). The Racadot et al reference goes on to say that [t]he use of anti-TNF mAb before infusion of muromonab-CD3 induces a clear down-regulation of this phenomenon and reduces the clinical manifestations of intolerance" (page 205, first column). Therefore, taken in view of the Chatenoud et al reference's teaching regarding success with non-mitogenic anti-CD3 $F(ab')_2$ fragments, one would have reasonably expected the induction of clonal anergy (nonresponsiveness) seen by Racadot et al (page 202, second paragraph) without the massive detrimental cytokine release associated with intact muromonab-CD3. Further, Racadot et al invites the humanization of murine antibodies (page 205, paragraph bridging columns) to alleviate the human-anti-murine-antibody response seen with treatment of human patients with murine antibodies and Güssow et al teaches that full humanization of murine antibodies is even more effective than the chimerization (pages 99-100) suggested by Racadot et al (page 205, paragraph bridging columns).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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F. Pierre VanderVegt, Ph.D.
January 18, 2000